REMARKS

Claims 29-34 are pending in the subject application. By this Amendment, applicant has amended claims 29 and 30. Applicant notes that the amendments to claims 29 and 30 are fully supported in the specification at, *inter alia*, page 29, lines 7-14 and 30-33; page 35, lines 2-7, and page 37, line 36 to page 38, line 13. Thus, applicant maintains that these amendments do not raise any issue of new matter. Accordingly, applicant respectfully requests that the Examiner enter this Amendment. Upon entry of this Amendment, claims 29-34, as amended, will be pending and under examination.

In view of the arguments set forth below, applicant respectfully submits that the Examiner's rejections made in the January 14, 2005 Final Office Action have been overcome. Applicant therefore requests that the Examiner reconsider and withdraw these rejections.

The Invention

The claimed invention provides methods of producing a monoclonal antibody from a tetroma cell formed by fusing a lymphoid cell capable of producing antibody with a trioma cell which does not produce any antibody, wherein the trioma cell is obtained by fusing a heteromyeloma cell which does not produce any antibody with a human lymphoid cell. The heteromyeloma cell used in this invention is obtained by fusing a human antibody-nonproducing myeloma cell with a mouse antibody-nonproducing myeloma cell. The use of such a heteromyeloma cell to generate the fusion partner trioma cell was neither known nor suggested in the prior art.

Rejections under 35 U.S.C. §103(a)

The Examiner rejected claims 29-33 under 35 U.S.C. §103(a) as

allegedly unpatentable over Oestberg et al. (U.S. Patent No. 4,634,664; "Oestberg") in view of Gustafsson et al. (Hum. Antibod. Hybridomas [1991] 2: 26-32; "Gustafsson") and Carroll et al. (J. Immunol. Methods [1986] 89: 61-72; "Carroll"). The Examiner stated that applicant's arguments have been considered and deemed not persuasive.

The Examiner stated that Oestberg teaches xenogeneic hybridoma fusion partners that do not produce antibody and the use of said cells as fusion partners to produce monoclonal antibodies upon fusion with an antibody-producing cell (citing column 2, last paragraph and column 3). The Examiner also stated that Oestberg teaches that the antibody-nonproducing xenogeneic hybridoma fusion partner can be made by fusing a myeloma cell to a human lymphocyte (citing column 2, last paragraph, continued on column 3). The Examiner further stated that Oestberg teaches that the myeloma cell used can be a hybrid cell formed from the fusion of two cells (citing column 2, last paragraph). The Examiner concluded that Oestberg thus teaches use of a three-cell-containing xenogeneic hybridoma fusion partner that does not produce antibody and the use of said cells as fusion partners to produce monoclonal antibodies. The Examiner acknowledged that Oestberg does not teach that their fusion partner cell is a trioma as per the definition of the term in the specification (e.g., "trioma" as a cell line formed from the fusion of three cells wherein a human-murine hybridoma is fused with a human lymphoid cell). The Examiner also noted that the human-murine hybridoma used in the trioma as defined in the specification could not produce antibody, allegedly because such a cell could not be used as a fusion partner.

The Examiner stated that Oestberg teaches heteromyeloma cell fusion partners (e.g., mouse myeloma/human fused cells, citing claim 14). The Examiner also stated that Gustafsson discloses that the term heteromyeloma encompasses a mouse myeloma cell fused to a

human PBL (citing the Abstract). The Examiner asserted that said heteromyeloma would be the same as the antibody-nonproducing human-murine hybridoma used in the trioma as defined in the specification. The Examiner concluded that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced the claimed method because (1) Oestberg teaches the claimed method except for use of a trioma cell line formed from the fusion of three cells, wherein a human-murine hybridoma is fused with a human lymphoid cell; (2) Oestberg teaches use of a three-cell antibody-nonproducing xenogeneic hybridoma fusion partner containing a hybrid myeloma cell; and (3) Oestberg and Gustafsson both teach human heteromyeloma cells (mouse-human hybrid myeloma cell lines).

The Examiner stated that one of ordinary skill in the art would have been motivated to produce the claimed method because Oestberg teaches use of hybrid myelomas as the fusion partner with an antibody-nonsecreting human lymphocyte (citing column 2, last paragraph, continued on next page) to form a three-cell antibody-nonsecreting fusion partner, and Oestberg and Gustafsson both teach heteromyeloma cell fusion partners (e.g., mouse-human fused cells). The Examiner also stated that the antibody-producing hybrid cells can be used *in vitro* or *in vivo* to produce antibody (citing claim 18). The Examiner further stated that the cells are grown *in vitro* under conditions in which antibody is produced (citing the Examples). The Examiner additionally stated that Oestberg teaches freeze storage of desired antibody secreting cells (citing column 7, penultimate paragraph).

In addition, the Examiner stated that the various assay steps recited in claim 30 involve steps known in the art for immunoassays (citing the Examples in Oestberg, and Gustafsson). The Examiner also stated that the use of a negative control in

immunoassays (e.g., a sample not containing the antigen as a background control) as a basis of comparison to a positive result is well known in the art (citing, for example, Gustafsson, page 28, column 1, Immunoglobulin-ELISA). The Examiner further stated that the condition recited in claim 30 could be any of the diseases known in the art which are disclosed in column 4 of Oestberg.

The Examiner also stated that Carroll discloses that a "heteromyeloma" encompasses a mouse myeloma/human PBL hybrid cell line (citing page 62, second column, last paragraph, continued on page 63, and Table 1, wherein SBC/H2O is referred to as a heteromyeloma). The Examiner further asserted that Carroll also uses the terms "heterohybridoma" and "heteromyeloma" interchangeably (citing the abstract and Table 1, wherein K6H6/B5 is disclosed as a heterohybridoma in the abstract, and as a heteromyeloma in Table 1).

The Examiner has Not Established a *Prima Facie* Case of Obviousness of Claims 29 and 30

In response, applicant respectfully traverses the above rejections.

Applicant notes that under M.P.E.P. §2142, the Examiner bears the initial burden of factually establishing a *prima facie* case of obviousness, and to do so, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge of a skilled artisan, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference, or references when combined, must teach or suggest all the claim limitations.

Applicant maintains that the Examiner fails to satisfy all three prongs of the requirements for establishing a *prima facie* case of obviousness under M.P.E.P. §2142. First, neither Oestberg alone,

nor in combination with Gustafsson and Carroll, provides any suggestion or motivation to make the subject invention comprising use of a heteromyeloma cell, formed by fusing a human antibody-nonproducing myeloma cell with a mouse antibody-nonproducing myeloma cell, to generate a trioma fusion partner cell. Second, a combination of these cited references does not provide any expectation of success in so using such a heteromyeloma cell. Third, the cited references in combination do not teach the claimed elements of the use of a trioma fusion partner cell derived from fusion of a heteromyeloma cell, which in turn is obtained by fusing a human antibody-nonproducing myeloma cell with a mouse antibody-nonproducing myeloma cell, in making the invention.

With regard to this third requirement, applicant notes that the trioma cell recited in claims 29 and 30, as amended, is made in relevant part by first fusing a human antibody-nonproducing myeloma cell with a mouse antibody-nonproducing myeloma cell to form an antibody-nonproducing heteromyeloma (human x mouse) cell (see the specification at, *inter alia*, page 29, lines 7-14 and 30-33; and page 35, lines 2-7). This heteromyeloma cell is then fused with a human lymphoid cell to form a trioma fusion partner cell (human x [human x mouse]). Fusion of an antibody-nonproducing variant of the trioma fusion partner cell with a human PBL generates an antibody-secreting tetroma (human x [human x {human x mouse}]) cell.

By contrast, Oestberg teaches the use of a "xenogeneic hybridoma cell" as a fusion partner cell. This cell, e.g., SPAZ-4, is an antibody-nonproducing variant of the hybrid cells formed by the fusion of the mouse SP-2 myeloma cell (which itself is a mouse myeloma/mouse lymphocyte hybrid) with a human PBL (see Oestberg et al., column 2, last paragraph, continued on column 3). Accordingly, the "xenogeneic hybridoma cell" taught by Oestberg et al. is not a heteromyeloma cell as defined in claims 29 and 30, as amended. Moreover, Oestberg's "xenogeneic hybridoma" fusion

partner (human x [mouse x mouse]) cell has a lower human genetic constitution than that of applicant's trioma fusion partner (human x [human x mouse]) cell. Thus, applicant maintains that at least two elements of the claimed invention are not taught by Oestberg: (1) the use of a heteromyeloma cell, obtained by fusing a human antibody-nonproducing myeloma cell with a mouse antibody-nonproducing myeloma cell; and (2) the generation of a trioma fusion partner cell line with a high human genetic constitution comparable to that of the trioma cell recited in the pending claims.

Applicant notes that Gustafsson describes the fusion of mouse myeloma cells with human PBL to form a hybrid (human x mouse) cell line, designated a "heteromyeloma" cell line (see, *inter alia*, the Abstract; and page 27, col. 1, last paragraph). This "heteromyeloma" may then be fused with human spleen cells or Epstein Barr virus (EBV)-transformed B-lymphocytes to produce antibody-secreting trioma (human x [human x mouse]) cells (see, *inter alia*, pages 26-27, bridging paragraph; and page 27, col. 1, last paragraph). Thus, applicant maintains that, similar to Oestberg's xenogeneic hybridoma, Gustafsson's "heteromyeloma" does not satisfy the definition of a heteromyeloma as recited in amended claims 29 and 30. Further, similar to Oestberg's xenogeneic hybridoma, Gustafsson's "heteromyeloma" (human x mouse) fusion partner cell has a human genetic constitution which is less than that of the trioma (human x [human x mouse]) fusion partner cell of the claimed invention.

Applicant notes also that Carroll describes the formation of hybrid (human x mouse) cell lines, designated heteromyelomas or heterohybridomas, from fusion of malignant, human lymphoid cells or human PBL with mouse myeloma cells (see, *inter alia*, page 62, col. 2, second paragraph; and page 62, Table 1). Antibody-nonsecreting variants (see page 63, col. 1, second paragraph) of these heteromyeloma/heterohybridoma lines are then used as fusion partner

cells with human B cell tumors to generate antibody-secreting trioma (human x [human x mouse]) cells (see, *inter alia*, the Abstract). Applicant notes that, similar to Oestberg's xenogeneic hybridoma and Gustafsson's "heteromyeloma" but unlike the heteromyeloma cells employed in the claimed invention, the heteromyeloma/heterohybridoma lines disclosed by Carroll are used as fusion partner cells. That is, they are fused with human lymphoid cells to produce antibody-secreting hybridoma cells. Also, similar to Oestberg's xenogeneic hybridoma and Gustafsson's "heteromyeloma," Carroll's fusion partner (human x mouse) cell has a lower human genetic constitution than that of the trioma (human x [human x mouse]) fusion partner cells of the claimed invention.

Applicant asserts, therefore, that at least two elements of the claimed invention, which are not taught by Oestberg, are also not taught by Gustafsson and Carroll. Applicant also reiterates that none of the Oestberg, Gustafsson or Carroll references, singly or in combination, provides any suggestion or motivation to make the subject invention using a heteromyeloma and a trioma cell as defined in claims 29 and 30, as amended, nor do these references provide any expectation of success in using such heteromyeloma and trioma cells.

The Claimed Methods and Prior Art Methods are Significantly Different

Applicant notes that the Examiner has maintained his position that the terms "heteromyeloma" and "heterohybridoma" are used interchangeably in the specification and in the relevant art. In response, and though still maintaining the incorrectness of the Examiner's position, applicant contends that the language describing "heteromyeloma" in amended claims 29 and 30, as obtained by fusing a human antibody-nonproducing myeloma cell with a mouse antibody-nonproducing myeloma cell, renders the Examiner's arguments moot.

In addition, applicant emphasizes that beyond the difference in the type of "heteromyeloma" cell used, there is at least one other substantive difference between his claimed method and those disclosed in the cited prior art references. In this regard, applicant notes that the hybrid cells disclosed by Oestberg (human x [mouse x mouse]), Gustafsson (human x mouse, and Carroll (human x mouse), irrespective of their nomenclature, are used as fusion partner cells, i.e., they are used for fusion with human lymphoid cells to generate antibody-secreting hybridoma cells. By contrast, the heteromyeloma cell recited in the pending claims is fused with a human lymphoid cell to generate a trioma cell, and it is this trioma (human x [human x mouse]) cell which is then used as a fusion partner cell for fusion with a lymphoid cell to produce an antibody-secreting hybridoma cell. Applicant emphasizes that the "trioma" defined in the specification is not merely a cell derived from the fusion of *any* three cells, but rather is derived from the fusion of a human-murine hybrid cell and a human lymphoid cell. Applicant maintains that by focusing on "trioma" as simply indicating a three-cell origin, the Examiner has overlooked important differences between Oestberg's three-cell-derived fusion partner cell and the trioma fusion partner cell recited in the pending claims.

Fusion of the trioma fusion partner cell with a human PBL generates an antibody-secreting tetroma (human x [human x {human x mouse}]) cell. Applicant notes that the genetic background of this tetroma has a human component which is more than twice as high as that in Oestberg's antibody-secreting hybridoma (human x [human x {mouse x mouse}]) cell line. Applicant asserts that the higher human genetic constitution of the trioma fusion partner cell recited in the pending claims, compared to Oestberg's fusion partner cell, confers important advantages for the production of human monoclonal antibodies.

Examiner's Response to Applicant' Remarks in Previous Communication

The Examiner stated that applicant has argued that Oestberg teaches use of a heterohybridoma, not a heteromyeloma. The Examiner also stated that the specification does not specifically define the terms heteromyeloma or heterohybridoma, but that the two terms (human-murine hybridoma (a.k.a. heterohybridoma) and heteromyeloma) are used interchangeably. The Examiner further stated that the Gustafsson reference specifically teaches that a heteromyeloma is formed by fusion of mouse myeloma cells and human PBLs. The Examiner additionally stated that Carroll discloses that a "heteromyeloma" encompasses a mouse myeloma/human PBL hybrid cell line, and also uses the terms "heterohybridoma" and "heteromyeloma" interchangeably.

The Examiner stated, regarding applicant's comments about Exhibit A supplied with applicant's October 25, 2004 Amendment, that this Exhibit refers to a web page from an unknown author with unknown credentials, and that there is no evidence of record to establish that the author is one of skill in the art. However, the Examiner asserted that the Carroll and Gustafsson publications are both published in peer-reviewed journals by authors who are of ordinary skill in the art. The Examiner also stated that the Gustafsson and Carroll references specifically teach that a heteromyeloma is formed by fusion of mouse myeloma cells and human PBLs.

The Examiner stated, regarding the cited passage on page 2 of the specification, that this passage does not disclose or define the term "heterohybridoma." The Examiner also stated, regarding applicant's comments about specific examples disclosed in the specification, that while these examples may disclose human myeloma/mouse myeloma hybrid cells, the term heteromyeloma is not disclosed in the specification as only encompassing such cells and the prior art clearly indicates that heteromyeloma encompasses

mouse myeloma/human PBL hybrid cells.

The Examiner also stated, regarding applicant's comments about what the claimed invention encompasses, that the prior art rejection addresses the invention as recited in the claims under consideration. The Examiner further stated that the claimed invention recites use of a heteromyeloma cell, which is rendered obvious for the reasons stated above. The Examiner noted that the claims under consideration do not recite that the heteromyeloma must be formed between two tumor cells. The Examiner also noted that the only functional property of the heteromyeloma recited in the claims under consideration is that it does not secrete antibody. The Examiner asserted, regarding applicant's various comments about the functional properties of the cell lines disclosed in the Examples section, as per above, that the instant rejection addresses the currently claimed invention recited in the claims under consideration.

In response, and without conceding the correctness of the Examiner's position, applicant again notes that independent claims 29 and 30, as hereinabove amended, specify that the heteromyeloma cell is obtained by fusing a human antibody-nonproducing myeloma cell with a mouse antibody-nonproducing myeloma cell. Applicant reiterates that the "xenogeneic hybridoma cell" taught by Oestberg and the "heteromyeloma" cell taught by Gustafsson are <u>not</u> heteromyeloma cells as defined in claims 29 and 30, as amended. Thus, applicant maintains that the Examiner's above comments are moot.

Applicant respectfully submits that his remarks and arguments made hereinabove obviate the rejections of claims 29 and 30 under 35 U.S.C. §103(a), and requests that the Examiner reconsider and withdraw these rejections.

Claims 31-33

Claims 31-33 depend, directly or indirectly, from claim 29 and therefore necessarily contain all the elements of claim 29, as amended. Applicant therefore submits that the remarks made hereinabove in relation to claims 29 and 30 also obviate the rejections of claims 31-33. Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw the rejections of claims 31-33.

Objection

The Examiner stated that claim 34 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form.

In response, applicant respectfully submits that based on the remarks made hereinabove, the rejection of base claim 29 should be withdrawn, thereby rendering the instant objection moot.

Conclusion

In view of the remarks and arguments set forth above, applicant respectfully requests that the Examiner reconsider and withdraw the rejections set forth in the January 14, 2005 Final Office Action, and earnestly solicits allowance of claims 29-34, as amended, pending in the subject application.

If a telephone conference would be of assistance in advancing the prosecution of the subject application, applicant's undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this

Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop AF, Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313-1450

3/14/02

Alan J. Morrison Date
Reg. No. 37,399

John P. White
Registration No. 28,678
Alan J. Morrison
Registration No. 37,399
Attorneys for Applicant
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400